WHAT IS CLAIMED IS:

1. A pharmacologically active peptide conjugate having a reduced tendency towards enzymatic cleavage comprising X and Z,

5 wherein X is a pharmacologically active peptide sequence, and

wherein Z is a stabilising peptide sequence, of 4-20 amino acid units covalently bound to X, wherein each amino acid unit in said stabilising peptide sequence, Z is selected from the 10 group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

15 wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and 20 carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring, e.g. 2,4-diaminobutanoic acid and 2,3-diaminopropanoic acid; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the 25 corresponding pharmacologically active peptide sequence, X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2, preferably at least about 3, such as at least about 5, more preferably at least about 7, such as at least about 9, e.g. at least about 10 or when said pharmacologically active peptide X is not orally 30 absorbed, said conjugate is absorbed,

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or a salt thereof, with the proviso that said pharmacologically active peptide conjugate is not selected from

H-Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu-(Lys-Glu)$_3$-OH,

H-Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu-(Glu)$_6$-OH,

5   H-Tyr-Gly-Gly-Phe-Leu-(Glu)$_6$-OH and

H-Tyr-Gly-Gly-Phe-Leu-(Lys)$_6$-OH.

2.   A peptide conjugate according to claim 1, wherein Z is covalently bound to X at the C-terminal carbonyl function of X.

10

3.   A peptide conjugate according to claim 1, wherein Z is covalently bound to the N-terminal nitrogen atom of X.

4.   A peptide conjugate according to claim 1, wherein the first sequence (Z) is covalently

15   bound to X at the C-terminal carbonyl function of X and the second sequence (Z) is covalently bound to the N-terminal nitrogen atom of X.

5.   A peptide conjugate according to claim 1, wherein Z is covalently bound to a nitrogen atom on the side chain of a lysine, arginine or histidine residue or a carbonyl function on the

20   side chain of glutamic acid or aspartic acid of X.

6.   A peptide conjugate according to claim 1, wherein Z consists of 4-15, preferably 4-10, more preferably 4-7, such as 6 amino acid units.

25 7.   A peptide conjugate according to claim 6, wherein each amino acid unit in Z is independently selected from the group consisting of Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Orn, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid and Met.

8.   A peptide conjugate according to claim 7, wherein each amino acid unit in Z is

30   selected from the group consisting of Glu, Lys and Met.

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9.   A peptide conjugate according to ~~any of claims 5 to 8~~ claim 1, wherein Z comprises at least one Lys amino acid unit, preferably at least two Lys amino acid units, such as at least three Lys amino acid units, e.g. at least four Lys amino acid units, more preferably at least five Lys amino acid units, such as six Lys amino acid units.

10.   A peptide conjugate according to claim 9, wherein Z is $(Lys)_n$, wherein n is an integer in the range from 4 to 15, preferably in the range from 4 to 10, such as in the range from 4 to 8, e.g. in the range from 4 to 6.

11.)   A peptide conjugate according to claim 9, wherein Z is Lys_4, Lys_5 or Lys_6.

12.   A peptide conjugate according to claim 11, wherein Z is Lys_6.

13.   A peptide conjugate according to ~~any of claims 5 to 9~~ claim 1, wherein Z is $(Lys-Xaa)_m$ or $(Xaa-Lys)_m$, wherein m is an integer in the range from 2 to 7, and each Xaa is independently selected from the group consisting of Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Arg, His, Orn, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid and Met.

14.   A peptide conjugate according to claim 13, wherein Z is $(Lys-Xaa)_3$ or $(Xaa-Lys)_3$, wherein each Xaa is independently selected from the group consisting of Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Arg, His, Orn, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid and Met.

15.   A peptide conjugate according to claim 15, wherein Z is $(Lys-Glu)_3$ or $(Glu-Lys)_3$.

16.   A peptide conjugate according to ~~any of claims 5 to 9~~ claim 1, wherein Z is Lys_p-Xaa_q or Xaa_p-Lys_q, wherein p and q are integers in the range from 1 to 14, with the proviso that p+q is in the range of 3-15, and each Xaa is independently selected from the group consisting of Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Arg, His, Orn, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid and Met.

17. A peptide conjugate according to claim 16, wherein Z is Lys$_3$-Xaa$_3$ or Xaa$_3$-Lys$_3$, wherein each Xaa is independently selected from the group consisting of Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Arg, His, Orn, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid and Met.

5   18. A peptide conjugate according to claim 17, wherein Z is Lys$_3$-Glu$_3$ or Glu$_3$-Lys$_3$,

19. A peptide conjugate according to claims 5-18, wherein Z is Lys-Lys-Lys-Lys, Xaa-Lys-Lys-Lys, Lys-Xaa-Lys-Lys, Lys-Lys-Xaa-Lys, Lys-Lys-Lys-Xaa, Xaa-Xaa-Lys-Lys, Xaa-
10 Lys-Xaa-Lys, Xaa-Lys-Lys-Xaa, Lys-Xaa-Xaa-Lys, Lys-Xaa-Lys-Xaa, Lys-Lys-Xaa-Xaa, Xaa-Xaa-Xaa-Lys, Xaa-Xaa-Lys-Xaa, Xaa-Lys-Xaa-Xaa, Lys-Xaa-Xaa-Xaa, Xaa-Xaa-Xaa-Xaa, Lys-Lys-Lys-Lys-Lys, Xaa-Lys-Lys-Lys-Lys, Lys-Xaa-Lys-Lys-Lys, Lys-Lys-Xaa-Lys-Lys, Lys-Lys-Lys-Xaa-Lys, Lys-Lys-Lys-Lys-Xaa, Xaa-Xaa-Lys-Lys-Lys, Xaa-Lys-Xaa-Lys-Lys, Xaa-Lys-Lys-Xaa-Lys, Xaa-Lys-Lys-Lys-Xaa, Lys-Xaa-Xaa-Lys-Lys,
15 Lys-Xaa-Lys-Xaa-Lys, Lys-Xaa-Lys-Lys-Xaa, Lys-Lys-Xaa-Xaa-Lys, Lys-Lys-Xaa-Lys-Xaa, Lys-Lys-Lys-Xaa-Xaa, Lys-Lys-Xaa-Xaa-Xaa, Lys-Xaa-Lys-Xaa-Xaa, Lys-Xaa-Xaa-Lys-Xaa, Lys-Xaa-Xaa-Xaa-Lys, Xaa-Lys-Lys-Xaa-Xaa, Xaa-Lys-Xaa-Xaa-Lys, Xaa-Xaa-Lys-Lys-Xaa, Xaa-Xaa-Lys-Xaa-Lys, Xaa-Xaa-Xaa-Lys-Lys, Lys-Xaa-Xaa-Xaa-Xaa, Xaa-Lys-Xaa-Xaa-Xaa, Xaa-Xaa-Lys-Xaa-Xaa, Xaa-Xaa-Xaa-Lys-Xaa, Xaa-Xaa-Xaa-Xaa-Lys,
20 Xaa-Xaa-Xaa-Xaa-Xaa, Lys-Lys-Lys-Lys-Lys-Lys, Xaa-Lys-Lys-Lys-Lys-Lys, Lys-Xaa-Lys-Lys-Lys-Lys, Lys-Lys-Xaa-Lys-Lys-Lys, Lys-Lys-Lys-Xaa-Lys-Lys, Lys-Lys-Lys-Lys-Xaa-Lys, Lys-Lys-Lys-Lys-Lys-Xaa, Xaa-Xaa-Lys-Lys-Lys-Lys, Xaa-Lys-Xaa-Lys-Lys-Lys, Xaa-Lys-Lys-Xaa-Lys-Lys, Xaa-Lys-Lys-Lys-Xaa-Lys, Xaa-Lys-Lys-Lys-Lys-Xaa, Lys-Xaa-Xaa-Lys-Lys-Lys, Lys-Xaa-Lys-Xaa-Lys-Lys, Lys-Xaa-Lys-Lys-Xaa-Lys,
25 Lys-Xaa-Lys-Lys-Lys-Xaa, Lys-Lys-Xaa-Xaa-Lys-Lys, Lys-Lys-Xaa-Lys-Xaa-Lys, Lys-Lys-Xaa-Lys-Lys-Xaa, Lys-Lys-Lys-Xaa-Xaa-Lys, Lys-Lys-Lys-Xaa-Lys-Xaa, Lys-Lys-Lys-Lys-Xaa-Xaa, Xaa-Xaa-Xaa-Lys-Lys-Lys, Xaa-Xaa-Lys-Xaa-Lys-Lys, Xaa-Xaa-Lys-Lys-Xaa-Lys, Xaa-Xaa-Lys-Lys-Lys-Xaa, Xaa-Lys-Xaa-Xaa-Lys-Lys, Xaa-Lys-Xaa-Lys-Xaa-Lys, Xaa-Lys-Xaa-Lys-Lys-Xaa, Xaa-Lys-Lys-Xaa-Xaa-Lys, Xaa-Lys-Lys-Xaa-Lys-Xaa, Xaa-Lys-Lys-Lys-Xaa-Xaa, Xaa-Lys-Lys-Xaa-Lys-
30 Xaa, Xaa-Lys-Lys-Lys-Xaa-Xaa, Lys-Lys-Lys-Xaa-Xaa-Xaa, Lys-Lys-Xaa-Lys-Xaa-Xaa, Lys-Lys-Xaa-Xaa-Lys-Xaa, Lys-Lys-Xaa-Xaa-Xaa-Lys, Lys-Xaa-Lys-Lys-Xaa-Xaa, Lys-Xaa-Lys-Xaa-Lys-Xaa, Lys-Xaa-Lys-Xaa-Xaa-Lys, Lys-Xaa-Xaa-Lys-Lys-Xaa, Lys-Xaa-

Xaa-Lys-Xaa-Lys, Lys-Xaa-Xaa-Xaa-Lys-Lys, Lys-Lys-Xaa-Xaa-Xaa-Xaa, Lys-Xaa-Lys-Xaa-Xaa-Xaa, Lys-Xaa-Xaa-Lys-Xaa-Xaa, Lys-Xaa-Xaa-Xaa-Lys-Xaa, Lys-Xaa-Xaa-Xaa-Xaa-Lys, Xaa-Lys-Lys-Xaa-Xaa-Xaa, Xaa-Lys-Xaa-Lys-Xaa-Xaa, Xaa-Lys-Xaa-Xaa-Lys-Xaa, Xaa-Lys-Xaa-Xaa-Xaa-Lys, Xaa-Xaa-Lys-Lys-Xaa-Xaa, Xaa-Xaa-Lys-Xaa-Lys-Xaa,

5 Xaa-Xaa-Lys-Xaa-Xaa-Lys, Xaa-Xaa-Xaa-Lys-Lys-Xaa, Xaa-Xaa-Xaa-Lys-Lys-Lys, Xaa-Xaa-Lys-Xaa-Lys, Xaa-Xaa-Xaa-Xaa-Lys-Lys, Lys-Xaa-Xaa-Xaa-Xaa-Xaa, Xaa-Lys-Xaa-Xaa-Xaa, Xaa-Xaa-Lys-Xaa-Xaa-Xaa, Xaa-Xaa-Xaa-Lys-Xaa-Xaa, Xaa-Xaa-Xaa-Xaa-Lys-Xaa, Xaa-Xaa-Xaa-Xaa-Xaa-Lys, or Xaa-Xaa-Xaa-Xaa-Xaa-Xaa, wherein each Xaa is independently selected from the group consisting of Ala, Leu, Ser, Thr, Tyr,

10 Asn, Gln, Asp, Glu, Arg, His, Met, Orn, and amino acids of the formula I

$$-NH-C(R^1)(R^2)-C(=O)-$$ (I)

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl,

15 and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a

20 cyclopentyl, cyclohexyl, or cycloheptyl ring, e.g. 2,4-diaminobutanoic acid (Dbu) and 2,3-diaminopropanoic acid (Dpr).

Claim 1

20. A peptide conjugate according to ~~any of claims 5 to 18~~, wherein Z consists of L-amino acids only.

Claim 1

25 21. A peptide conjugate according to ~~any of claims 5-7~~, wherein Z is (Dbu)$_n$ or (Dpr)$_n$, wherein n is an integer in the range from 4 to 15, preferably in the range from 4 to 10, such as in the range from 4 to 8, e.g. in the range from 4 to 6.

30 22. A peptide conjugate according to claim 1, wherein Z is Dpr$_6$.

23. A peptide conjugate according to any of the preceding claims, wherein said pharmacologically active peptide sequence (X) consists of at the most 75 amino acid units, such as at the most 65, e.g. a the most 60, preferably at the most 55, such as at the most 53, e.g. at the most 50.

24. The peptide conjugate according to claim 16, wherein X is selected from the group consisting of enkephalin, Leu-enkephalin, Met-enkephalin, angiotensin I, angiotensin II, vasopressin, endothelin, vasoactive intestinal peptide, neurotensin, endorphins, insulin, gramicidin, paracelsin, delta-sleep inducing peptide, gonadotropin-Releasing hormone,

10 human parathyroid hormone (1-34), truncated erythropoietin analogues, specifically EMP-1, Atrial natriuretic peptide (ANP, ANF), human brain natriuretic peptide (hBNP), cecropin, kinetensin, neurophysins, elafin, guamerin, atriopeptin I, atriopeptin II, atriopeptin III, deltorphin I, deltorphin II, vasotocin, bradykinin, dynorphin, dynorphin A, dynorphin B, growth hormone release factor, growth hormone, growth hormone releasing peptide,

15 oxytocin, calcitonin, calcitonin gene-related peptide, calcitonin gene-related peptide II, growth hormone releasing peptide, tachykinin, adrenocorticotropic hormone (ACTH), brain natriuretic polypeptide, cholecystokinin, corticotropin releasing factor, diazepam binding inhibitor fragment, FMRF-amide, galanin, gastric releasing polypeptide, gastric inhibitory polypeptide, gastrin, gastrin releasing peptide, glucagon, glucagon-like peptide-1, glucagon-

20 like peptide-2, LHRH, melanin concentrating hormone, melanocyte stimulating hormone (MSH), alpha-MSH, morphine modulating peptides, motilin, neurokinin A, neurokinin B, neuromedin B, neuromedin C, neuromedin K, neuromedin N, neuromedin U, neuropeptide K, neuropeptide Y, pituitary adenylate cyclase activating polypeptide (PACAP), pancreatic polypeptide, peptide YY, peptide histidine-methionine amide (PHM), secretin,

25 somatostatin, substance K, thyrotropin-releasing hormone (TRH), kyotorphin, melanostatin (MIF-1), thrombopoeitin analogs, in particular AF 12505 (Ile-Glu-Gly-Pro-Thr-Leu-Arg-Gln-Trp-Leu-Ala-Ala-Arg-Ala), insulin-like growth factor I (57-70) (Ala-Leu-Leu-Glu-Thr-Tyr-Cys-Ala-Thr-Pro-Ala-Lys-Ser-Glu), insulin-like growth factor I (30-41) (Gly-Tyr-Gly-Ser-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr), insulin-like growth factor I (24-41)(Tyr-Phe-

30 Asn-Lys-Pro-Thr-Gly-Tyr-Gly-Ser-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr) , insulin-like growth factor II (33-40) (Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg), insulin-like growth [tyro] factor II (33-40) (Tyr-Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg), insulin-like growth factor II (69-84)

(Asp-Val-Ser-Thr-Pro-Pro-Thr-Val-Leu-Pro-Asp-Asn-Phe-Pro- Arg-Tyr), growth hormone
(GH)-releasing peptide-6 (GHRP-6) (His-DTrp-Ala-Trp-DPhe-Lys-NH2), beta-Interleukin I
(163-171) (Val-Gln-Gly-Glu-Glu-Ser-Asn-Asp-Lys), beta-Interleukin II (44-56) (Ile-Leu-
Asn-Gly-Ile-Asn-Asn-Tyr-Lys-Asn-Pro-Lys-Leu), Interleukin II (60-70) (Leu-Thr-Phe-Lys-

5 Phe-Tyr-Met-Pro-Lys-Lys-Ala), exendin-4 (GLP-1 analog) (His-Gly-Glu-Gly-Thr-Phe-Thr-
Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-
Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2), exendin-3 (GLP-1 analog) (His-
Ser-Asp-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-
Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser),

10 [Cys(Acm)20,31] epidermal growth factor (20-31) Cys(Acm)-Met-His-Ile-Glu-Ser-Leu-
Asp-Ser-Tyr-Thr-Cys(Acm), bivalirudin (Hirulog) (D-Phe-Pro-Arg-Pro-(Gly)4-Asn-Gly-
Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu), hirulog-1 D-Phe-Pro-Arg-Pro-(Gly)4-Asn-
Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Tyr-Leu, C-type natriuretic peptide (1-53) (CNP) (Asp-
Leu-Arg-Val-Asp-Thr-Lys-Ser-Arg-Ala-Ala-Trp-Ala-Arg-Leu-Leu-Gln-Glu-His-Pro-Asn-

15 Ala-Arg-Lys-Tyr-Lys-Gly-Ala-Asn-Lys-Lys-Gly-Leu-Ser-Lys-Gly-Cys-Phe-Gly-Leu-Lys-
Leu-Asp-Arg-Ile-Gly-Ser-Met-Ser-Gly-Leu-Gly-Cys; Disulfide bridge: Cys37-Cys53),
"Mini ANP" (Met-Cys-His-cyclohexylAla-Gly-Gly-Arg-Met-Asp-Arg-Ile-Ser-Cys-Tyr-
Arg, disulfide bridge cys2-cys13), Melanotan-II (also known as MT-II, alpha-MSH4-10-
NH2, or Ac-Nle4-Asp5-His6-DPhe7-Arg8-Trp9-Lys10), thymosin alpha1 (TA1) (Ac-Ser-

20 Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Lys-Glu-
Val-Val-Glu-Glu-Ala-Glu-Asn), ornipressin (also known as 8-ornithine-vasopressin,
(POR-8), [Phe2,Ile3,Orn8]vasopressin), Cys-Phe-Ile-Gln-Asn-Cys-Pro-Orn-Gly-NH2,
Disulfide bridge: Cys1-Cys6), octreotide (201-995) (DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-
Thr-ol; disulfide bridge: Cys2-Cys7), eptifibatide (INTEGRILIN), calcitonin gene-related

25 peptide (CGRP) (Ala-Cys-Asp-Thr-Ala-Thr-Cys-Val-Thr-His-Arg-Leu-Ala-Gly-Leu-Leu-
Ser-Arg-Ser-Gly-Gly-Val-Val-Lys-Asn-Asn-Phe-Val-Pro-Thr-Asn-Val-Gly-Ser-Lys-Ala-
Phe-NH2; Disulfide bridge: Cys2-Cys7), endomorphin-1 Tyr-Pro-Trp-Phe-NH2;
endomorphin-2 Tyr-Pro-Phe-Phe-NH2, nociceptin (also known as Orphanin FQ, Phe-Gly-
Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln), angiotensinogen (1-

30 13) (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His), adrenomodullin (1-12) (Tyr-
Arg-Gln-Ser-Met-Asn-Asn-Phe-Gln-Gly-Leu-Arg), antiarrhytmic peptide (AAP) (Gly-Pro-
Hyp-Gly-Ala-Gly), Antagonist G (Arg-DTrp-(nMe)Phe-DTrp-Leu-Met-NH2), indolicidin

(Ile-Leu-Pro-Trp-Lys-Trp-Pro-Trp-Trp-Pro-Trp-Arg-Arg-NH₂), osteocalcin (37-49) (Gly-Phe-Gln-Glu-Ala-Tyr-Arg-Arg-Phe-Tyr-Gly-Pro-Val), cortistatin 29 (1-13) (Glp)-Glu-Arg-Pro-Pro-Leu-Gln-Gln-Pro-Pro-His-Arg-Asp), cortistatin 14 Pro-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Ser-Ser-Cys-Lys; Disulfide bridge: Cys2-Cys13, PD-145065 (Ac-D-Bhg-

5 Leu-Asp-Ile-Ile-Trp), PD-142893 (Ac-D-Dip-Leu-Asp-Ile-Ile-Trp), fibrinogen binding inhibitor peptide (His-His-Leu-Gly-Gly-Ala-Lys-Gln-Ala-Gly-Asp-Val), leptin (93-105) (Asn-Val-Ile-Gln-Ile-Ser-Asn-Asp-Leu-Glu-Asn-Leu-Arg), GR 83074 (Boc-Arg-Ala-DTrp-Phe-DPro-Pro-Nle-NH₂), Tyr-W-MIF-1 (Tyr-Pro-Trp-Gly-NH₂), parathyroid hormone related peptide (107-111) (Thr-Arg-Ser-Ala-Trp), angiotensinogen (1-14) Asp-

10 Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Asn, Leupeptin (Ac-Leu-Leu-Arg-CHO), and any modified or truncated analogue thereof.

25. A peptide conjugate according to any of the previous claims wherein the conjugate is

15 H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-Lys₆-NH₂ (GHRH(1-44)(Human)-Lys₆-NH₂);

H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-

20 Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-Glu₆-NH₂ (GHRH (1-44)(Human)-Glu₆-NH₂);

H- Lys₆-Ser-Val-Ser-Glu-Ile-Gln-Leu-Met-His-Asn-Leu-Gly-Lys-His-Leu-Asn-Ser-Met-Glu-Arg-Val-Glu-Trp-Leu-Arg-Lys-Lys-Leu-Gln-Asp-Val-His-Asn-Phe-OH (Lys₆-PTH(1-

25 34)(Human)-OH);

H-Ser-Val-Ser-Glu-Ile-Gln-Leu-Met-His-Asn-Leu-Gly-Lys-His-Leu-Asn-Ser-Met-Glu-Arg-Val-Glu-Trp-Leu-Arg-Lys-Lys-Leu-Gln-Asp-Val-His-Asn-Phe-Lys₆-OH (PTH(1-34)(Human)-Lys₆-OH);

30

H-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Lys₆-OH (GLP-1-(7-36)(Human)-Lys₆-OH);

H-Gly-Gly-Thr-Tyr-Ser-Cys(Acm)-His-Phe-Gly-Pro-Leu-Thr-Trp-Val-Cys(Acm)-Lys-Pro-Gln-Gly-Gly-Lys$_6$-OH (EMP-1-Lys$_6$-OH);

5 H-   Lys$_6$-Gly-Gly-Thr-Tyr-Ser-Cys(Acm)-His-Phe-Gly-Pro-Leu-Thr-Trp-Val-Cys(Acm)-Lys-Pro-Gln-Gly-Gly-OH (Lys$_6$-EMP-1-OH);

H-   Lys$_6$-Gly-Gly-Thr-Tyr-Ser-Cys(Acm)-His-Phe-Gly-Pro-Leu-Thr-Trp-Val-Cys(Acm)-Lys-Pro-Gln-Gly-Gly- Lys$_6$-OH (Lys$_6$-EMP-1- Lys$_6$-OH);

10

H-Aib-His-2-D-Nal-D-Phe-Lys-(Lys)$_6$-NH$_2$ (GHRP-(Lys)$_6$-NH$_2$);

H-Tyr-Gly-Gly-Phe-Leu-Lys-Lys-Glu-Glu-Glu-Lys--OH   (Leu-enkephalin-Lys-Lys-Glu-Glu-Glu-Lys-OH);

15

H-Tyr-Gly-Gly-Phe-Leu-Lys-Glu-Glu-Glu-Glu-Lys--OH   (Leu-enkephalin-Lys-Glu-Glu-Glu-Glu-Lys-OH);

H-Tyr-Gly-Gly-Phe-Leu-Lys-Glu-Glu-Glu-Glu-Lys--OH (Leu-enkephalin-(Lys-Glu)$_3$;

20

H-Tyr-Gly-Gly-Phe-Leu-(Dpr)$_6$-OH (Leu-enkephalin-(Dpr)$_6$-OH);

H-Lys$_6$-Tyr-Gly-Gly-Phe-Leu-OH (H-Lys$_6$-Leu-enkephalin);

25 H-Tyr-Gly-Gly-Phe-Leu- Lys$_6$-OH (H-Leu-enkephalin-Lys$_6$);

H-Lys$_6$-Tyr-Gly-Gly-Phe-Leu-Lys$_6$-OH (H-Lys$_6$-Leu-enkephalin-Lys$_6$-OH);

Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-(Lys)$_6$-OH (GnRH-Lys$_6$-OH);

30

Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-(Lys-Glu)$_3$-OH (GnRH-(Lys-Glu)$_3$-OH); and

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H-Ser-Val-Ser-Glu-Ile-Gln-Leu-Met-His-Asn-Leu-Gly-Lys-His-Leu-Asn-Ser-Met-Glu-
Arg-Val-Glu-Trp-Leu-Arg-Lys-Lys-Leu-Gln-Asp-Val-His-Asn-Phe-(Lys-Glu)₃-OH (PTH
1-34 human-(Lys-Glu)₃-OH).

5

26. A method for the preparation of a pharmacologically active peptide conjugate (X-Z) as
defined in claim 2, comprising the steps of:

a) coupling an N-α-protected amino acid   or N-α-protected dipeptide in the carboxyl
10 activated form, in the C-terminal activated form to an immobilised peptide sequence H-Z-
SSM, thereby forming an immobilised N-α-protected peptide fragment,

b) removing the N-α-protecting group, thereby forming an immobilised peptide fragment
having an unprotected N-terminal end,

15

c) coupling an additional N-α-protected amino acid in the carboxyl activated form, or an
additional N-α-protected dipeptide in the C-terminal activated form to the N-terminal end of
the immobilised peptide fragment, and repeating the removal/coupling step procedure in
step b) and c) until the desired peptide sequence X is obtained, and then

20

d) cleaving off the peptide conjugate from the solid support material.

27. A method for the preparation of a pharmacologically active peptide conjugate (Z-X) as
defined in claim 3, comprising the steps of:

25

a)   coupling an N-α-protected amino acid, or an N-α-protected dipeptide to a solid support
material (SSM), thereby forming an immobilised N-α-protected amino acid,

b)   removing the N-α-protecting group, thereby forming an immobilised amino acid or
30 peptide fragment having an unprotected N-terminal end,

c)   coupling an additional N-α-protected amino acid in the carboxyl activated form, or an additional N-α-protected dipeptide in the C-terminal activated form to the N-terminal end of the immobilised amino acid or peptide fragment, and repeating the removal/coupling step procedure in step b) and c) until the desired peptide sequence X is obtained,

5

d)   coupling an additional N-α-protected amino acid in the carboxyl activated form, or an additional N-α-protected dipeptide in the C-terminal activated form to the N-terminal end of the immobilised peptide fragment, and repeating the removal/coupling step procedure in step b) and d) until the desired peptide sequence Z is obtained, and then

10

e)   cleaving off the peptide conjugate from the solid support material.

28.   A method for the preparation of a pharmacologically active peptide conjugate (Z-X-Z) as defined in claim 4, comprising the steps of:

15

a)   coupling an N-α-protected amino acid in the carboxyl activated form, or an N-α-protected dipeptide in the C-terminal activated form to an immobilised peptide sequence H-Z-SSM, thereby forming an immobilised N-α-protected peptide fragment,

20 b)   removing the N-α-protecting group, thereby forming an immobilised peptide fragment having an unprotected N-terminal end,

c)   coupling an additional N-α-protected amino acid in the carboxyl activated form, or an additional N-α-protected dipeptide in the C-terminal activated form to the N-terminal end of
25   the immobilised peptide fragment, and repeating the removal/coupling step procedure in step b) and c) until the desired peptide sequence X is obtained, and then

d)   coupling an additional N-α-protected amino acid in the carboxyl activated form, or an additional N-α-protected dipeptide in the C-terminal activated form to the N-terminal end of
30   the immobilised peptide fragment, and repeating the removal/coupling step procedure in step b) and d) until the desired peptide sequence Z is obtained, and then

e) cleaving off the peptide conjugate from the solid support material.

29. A method for producing the peptide conjugate of claim 1, comprising

a) introducing a nucleic acid sequence encoding said conjugate into a host cell;

5 b) culturing said host cell and

c) isolating said conjugate from the culture.

30. A method for producing the peptide conjugate of claim 1, comprising

a) culturing a recombinant host cell comprising a nucleic acid sequence encoding said

10 conjugate under conditions permitting the production of said conjugate; and

b) isolating said conjugate from the culture.

31. The method according to claim 29 ~~or claim 30~~, wherein the nucleic acid sequence encoding said conjugate is contained within a nucleic acid construct or a vector.

15

32. A composition comprising a pharmacologically active peptide conjugate ~~as defined in~~ according to claim 1 ~~any of the claims 1-25~~, and a pharmaceutical acceptable carrier.

~~33. A composition comprising~~
20 ~~H-Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu-(Lys-Glu)₃-OH,~~
~~H-Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu-(Glu)₆-OH,~~
~~H-Tyr-Gly-Gly-Phe-Leu-(Glu)₆-OH or~~
~~H-Tyr-Gly-Gly-Phe-Leu-(Lys)₆-OH, and a pharmaceutical acceptable carrier.~~

25 34. A pharmacologically active peptide conjugate as defined in any of claims 1-26 for use in therapy.

35. A pharmacologically active peptide conjugate selected from the group consisting of
H-Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu-(Lys-Glu)₃-OH,
30 H-Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu-(Glu)₆-OH,
H-Tyr-Gly-Gly-Phe-Leu-(Glu)₆-OH and
H-Tyr-Gly-Gly-Phe-Leu-(Lys)₆-OH,

~~for use in therapy.~~

36. Use of a pharmacologically active peptide conjugate as defined in any of claims 1-25 for the manufacture of a pharmaceutical composition for use in treatment of pain, HIV,

5 cancer, diabetes, incontinence, hypertension, amnesia, Alzheimer's disease, fever, depression, sex-hormone regulation, eating, schizophrenia, osteoporosis and insomnia.

37. A method for inhibiting neurons from transmitting pain impulses to the spinal cord, comprising administering to a subject in need thereof a conjugate comprising enkephalin

10 and a stabilising sequence, Z of 4-20 amino acids covalently attached to X, wherein Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \qquad\qquad (I)$$

15

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents

20 selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring, e.g. 2,4-diaminobutanoic acid and 2,3-diaminopropanoic acid;

25 wherein the ratio between the half-life of said peptide conjugate and the half-life of enkephalin when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2, preferably at least about 3, such as at least about 5, more preferably at least about 7, such as at least about 9, e.g. at least about 10 or when X is inot orally absorbed said

30 peptide conjugate is orally absorbed in an amount effective to inhibit neurons from transmitting pain impulses.

38. Use of a conjugate comprising enkephalin and a stabilising sequence, Z of 4-20 amino acids covalently attached to X, wherein Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

5

$$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three

10 substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring, e.g. 2,4-diaminobutanoic acid and 2,3-

15 diaminopropanoic acid; and

Wherein the ratio between the half-life of said peptide conjugate and the half-life of enkephalin when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at

20 least about 2, preferably at least about 3, such as at least about 5, more preferably at least about 7, such as at least about 9, e.g. at least about 10 or when X is inot orally absorbed said peptide conjugate is orally absorbedfor the manufacture of a pharmaceutical composition for use in treatment of pain.

25 39. A method for stimulating the release of growth hormone from the pituitary comprising administering to a subject in need thereof a conjugate comprising growth hormone releasing hormone or growth hormone releasing peptide and a stabilising sequence, Z of 4-20 amino acids covalently attached to X, wherein Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the

30 general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and

5 phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring, e.g. 2,4-diaminobutanoic acid and 2,3-diaminopropanoic acid; and

10

Wherein the ratio between the half-life of said peptide conjugate and the half-life of growth hormone releasing hormone or growth hormone releasing peptide when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2, preferably at least

15 about 3, such as at least about 5, more preferably at least about 7, such as at least about 9, e.g. at least about 10 or when X is not orally absorbed said peptide conjugate is orally absorbed in an amount effective to stimulate the release of growth hormone.

40. Use of a conjugate comprising growth hormone releasing hormone or growth hormone

20 releasing peptide and a stabilising sequence, Z of 4-20 amino acids covalently attached to X, wherein Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \qquad\qquad (I)$$

25

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents

30 selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a

cyclopentyl, cyclohexyl, or cycloheptyl ring, e.g. 2,4-diaminobutanoic acid and 2,3-diaminopropanoic acid; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of growth
5 hormone releasing hormone or growth hormone releasing peptide when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2, preferably at least about 3, such as at least about 5, more preferably at least about 7, such as at least about 9, e.g. at least about 10 or when X is not orally absorbed, said peptide conjugate is orally
10 absorbed, for the manufacture of a pharmaceutical composition for use in stimulating the release of growth hormone.

41.   A method for increasing hemoglobin levels comprising administering to a subject in need thereof a conjugate comprising EMP-1 and a stabilising sequence, Z of 4-20 amino
15 acids covalently attached to X, wherein Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I
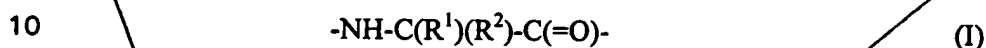
$$-NH-C(R^1)(R^2)-C(=O)-$$ (I)

20

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three
25 substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring, e.g. 2,4-diaminobutanoic acid and 2,3-diaminopropanoic acid; and

30 Wherein the ratio between the half-life of said peptide conjugate and the half-life of EMP-1 when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least

about 2, preferably at least about 3, such as at least about 5, more preferably at least about 7, such as at least about 9, e.g. at least about 10 or when X is not orally absorbed said peptide conjugate is orally absorbed in an amount effective to increase hemoglobin levels.

5   42.   Use of a conjugate comprising EMP-1 and a stabilising sequence, Z of 4-20 amino acids covalently attached to X, wherein Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

10    $$-NH-C(R^1)(R^2)-C(=O)-$$ (I)

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and

15   phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring, e.g. 2,4-diaminobutanoic acid and 2,3-diaminopropanoic acid;

20   wherein the ratio between the half-life of said peptide conjugate and the half-life of EMP-1 when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2, preferably at least about 3, such as at least about 5, more preferably at least about 7,

25   such as at least about 9, e.g. at least about 10 or when X is not orally absorbed said peptide conjugate is orally absorbed for the manufacture of a pharmaceutical composition for use in treating anemia by increasing hemoglobin levels.

43.   A method for preventing or treating bone loss by altering the balance between

30   ostoclastic and osteoblast activity comprising administering to a patient in need thereof a conjugate comprising parathyroid hormone and a stabilising sequence, Z of 4-20 amino acids covalently attached to X, wherein Z is selected from the group consisting of Ala, Leu,

Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \tag{I}$$

5

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents

10 selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring, e.g. 2,4-diaminobutanoic acid and 2,3-diaminopropanoic acid; and

15 Wherein the ratio between the half-life of said peptide conjugate and the half-life of parathyroid hormone when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2, preferably at least about 3, such as at least about 5, more preferably at least about 7, such as at least about 9, e.g. at least about 10 or when X is not orally absorbed

20 said peptide conjugate is orally absorbed in an amount effective to treat or prevent bone loss.

44. Use of a conjugate comprising parathyroid hormone and a stabilising sequence, Z of 4-20 amino acids covalently attached to X, wherein Z is selected from the group consisting of

25 Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \tag{I}$$

30 wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and

phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring, e.g. 2,4-diaminobutanoic acid and 2,3-

5 diaminopropanoic acid; and

Wherein the ratio between the half-life of said peptide conjugate and the half-life of parathyroid hormone when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma

10 is at least about 2, preferably at least about 3, such as at least about 5, more preferably at least about 7, such as at least about 9, e.g. at least about 10, or when X is not orally absorbed said peptide conjugate is orally absorbed, for the manufacture of a pharmaceutical composition for use in preventing or treating osteoporosis.

15 45. A method for reducing blood glucose levels comprising administering to a subject in need thereof a conjugate comprising glucagon-like peptide-1 and a stabilising sequence, Z of 4-20 amino acids covalently attached to X, wherein Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

20

$$-NH-C(R^1)(R^2)-C(=O)- \tag{I}$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three

25 substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring, e.g. 2,4-diaminobutanoic acid and 2,3-

30 diaminopropanoic acid; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of glucagon-like peptide-1 when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2, preferably at least about 3, such as at least about 5, more preferably at

5   least about 7, such as at least about 9, e.g. at least about 10 or when X is not orally absorbed said peptide conjugate is orally absorbed in an amount effective to reduce blood glucose levels.

46.   Use of a conjugate comprising glucagon-like peptide-1 and a stabilising sequence, Z of

10   4-20 amino acids covalently attached to X, wherein Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I
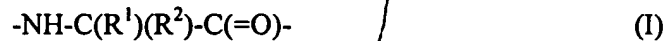
$$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

15

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents

20   selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring, e.g. 2,4-diaminobutanoic acid and 2,3-diaminopropanoic acid; and

25   wherein the ratio between the half-life of said peptide conjugate and the half-life of glucagon-like peptide-1 when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2, preferably at least about 3, such as at least about 5, more preferably at least about 7, such as at least about 9, e.g. at least about 10 or when X is not orally absorbed

30   said peptide conjugate is orally absorbed, for the manufacture of a pharmaceutical composition for use in treatment of diabetes.
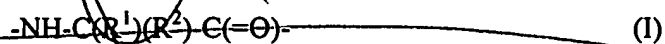
47. A method for regulating production of sex hormones comprising administering to a subject in need thereof a conjugate comprising gonadotropin releasing hormone and a stabilising sequence, Z of 4-20 amino acids covalently attached to X, wherein Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His,

5 Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)-\qquad\qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl,

10 and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a

15 cyclopentyl, cyclohexyl, or cycloheptyl ring, e.g. 2,4-diaminobutanoic acid and 2,3-diaminopropanoic acid; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of gonadotropin when treated with carboxypeptidase A or leucine aminopeptidase in about 50

20 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2, preferably at least about 3, such as at least about 5, more preferably at least about 7, such as at least about 9, e.g. at least about 10 or when X is not orally absorbed said peptide conjugate is orally absorbed in an amount effective to regulate production of sex hormones.
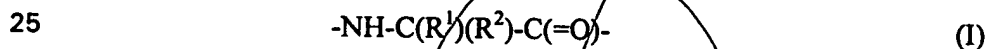
25

48. Use of a conjugate comprising gonadotropin releasing hormone and a stabilising sequence, Z of 4-20 amino acids covalently attached to X, wherein Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

30

$$-NH-C(R^1)(R^2)-C(=O)-\qquad\qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents

5   selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring, e.g. 2,4-diaminobutanoic acid and 2,3-diaminopropanoic acid; and

10   wherein the ratio between the half-life of said peptide conjugate and the half-life of gonadotropin releasing hormone when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2, preferably at least about 3, such as at least about 5, more preferably at least about 7, such as at least about 9, e.g. at least about 10 or when X is

15   not orally absorbed said peptide conjugate is orally absorbed and the ratio between the half-life of said peptide conjugate for the manufacture of a pharmaceutical composition for use in regulating the level of sex hormones.

49. A method for treating sleep disorders comprising administering to a subject in need

20   thereof a conjugate comprising delta sleep inducing peptide and a stabilising probe, Z of 4-20 amino acids covalently attached to X, wherein Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

25    $$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and

30   phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a

cyclopentyl, cyclohexyl, or cycloheptyl ring, e.g. 2,4-diaminobutanoic acid and 2,3-diaminopropanoic acid; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of delta-
5   sleep inducing peptide when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2, preferably at least about 3, such as at least about 5, more preferably at least about 7, such as at least about 9, e.g. at least about 10, or when the pharmacologically active peptide X is not orally absorbed, the conjugate will be orally absorbed, in an amount
10   effective to treat said sleep disorder.

50. Use of a conjugate comprising delta-sleep inducing peptide and a stabilising probe, Z of 4-20 amino acids covalently attached to X, wherein Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid
15   units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \hspace{3cm} (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-
20   alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound
25   form a cyclopentyl, cyclohexyl, or cycloheptyl ring, e.g. 2,4-diaminobutanoic acid and 2,3-diaminopropanoic acid; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of Substance P when treated with carboxypeptidase A or leucine aminopeptidase in about 50
30   mM phosphate buffer solution at about pH 7.4 at about 37°C and in serum or plasma is at least about 2, preferably at least about 3, such as at least about 5, more preferably at least about 7, such as at least about 9, e.g. at least about 10, or when the pharmacologically active

peptide X is not orally absorbed, the conjugate will be orally absorbed, for the manufacture of a pharmaceutical composition for use in treating a sleep disorder

51. Use of a stabilising peptide sequence (Z) of 4-20 amino acid units for the preparation of a pharmacologically active peptide conjugate as defined in any of claims 1-26,

each amino acid unit in said stabilising peptide sequence Z being independently selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, or amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)-$$ (I)

wherein R^1 and R^2 independently are selected from hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring;

or a salt thereof.

Add C-7

Add D^∞

Add H^10

Add H^13